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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/563,042	03/13/2006	Shubha Anand	BJS-620-406	8188

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NIXON & VANDERHYE, PC
901 NORTH GLEBE ROAD, 11TH FLOOR
ARLINGTON, VA 22203

EXAMINER	
LOVE, TREVOR M	
ART UNIT	PAPER NUMBER
1611	
MAIL DATE	DELIVERY MODE
01/14/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/563,042	ANAND ET AL.	
	Examiner	Art Unit	
	TREVOR M. LOVE	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 November 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) *10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgement is made to Applicant's response filed 11/11/2010.

Claims 1-10 are pending.

Claims 11-51 are cancelled.

Claim 10 remains withdrawn.

Claims 1-9 are currently under consideration.

No claims are currently amended.

Note: it is noted that in the previous Office Action in the response to arguments, there was an incorrect reference to Wang, wherein said reference was intended to recite Hauf. Applicant's identification of said clear typographical error is appreciated, and thereby ensuring the record is clear.

Maintained Rejections

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-5 and 8-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sen et al (1997, Oncogene) as evidenced by Entrez Gene (AURKA Aurora Kinase A) in view of Patel et al (2000, Oncogene) and Hauf et al (2003, Journal of Cell Biology) (IDS reference).

Sen teaches that human breast cancer exhibits an amplified and overexpressed amount of BTAK which is a serine/threonine kinase (see entire document, for instance, Title). Entrez Gene evidences that BTAK is also known as aurora kinase A (see entire document, for instance section labeled "Summary").

Sen fails to directly teach treating breast cancer with an Aurora A Kinase inhibitor, namely Hesperadin, or with a mitotic spindle assembly inhibitor, namely paclitaxel.

Patel teaches that paclitaxel is a microtubule-stabilizing agent, wherein cells exit mitosis aberrantly and fractionate into hypodiploid populations during cell cycle analysis (see entire document, for instance, page 4163, first column, first paragraph). Patel further teaches that breast cancer cells are sensitive to paclitaxel (see entire document, for instance, Title).

Hauf teaches that Hesperadin is an aurora A kinase inhibitor (see entire document, for instance page 284, column 2, last paragraph). Hauf proffers that Hesperadin treatment turned off checkpoint signaling in Taxol-treated cells because all kinetochores progressively accumulated stably attached microtubles. Hauf teaches that Hesperadin might allow cells treated with paclitaxel to exit the mitotic phase by stabilizing improper microtubule attachments (see entire document, for instance page 288, column 2, last sentence).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize the antineoplastic agent paclitaxel of Patel and the aurora A kinase inhibitor Hesperadin of Hauf to treat a patient with breast cancer, such as those of Sen. One would have been motivated to do so since both the paclitaxel of Patel and the Hesperadin of Hauf are directed to stabilizing microtubule attachment and exiting cells from mitosis wherein the exiting cell is in an aberrant or improper condition. Also, one would have been motivated to utilize the paclitaxel of Patel to treat the breast cancer of Sen since Patel teaches that breast cancer cells are sensitive to paclitaxel. There would be a reasonable expectation of success since both Sen and Patel are

directly drawn to breast cancer, and Sen identifies a clear nexus between aurora A kinase and breast cancer.

Response to Arguments and Declaration

Applicant argues in the remarks filed 11/11/2010 that the references fail to teach or suggest how to overcome the resistance to Aurora A over-expression in cells. Applicant further argues that one of ordinary skill in the art would not utilize an aurora A inhibitor absent a clear teaching in the art as to the effect of Aurora A over-expression with regard to paclitaxel-resistance. Applicant's arguments are not found persuasive since first, the references would lead one of ordinary skill in the art to the treatment of a patient with breast cancer comprising treating said patient with Taxol and Hesperadin. Second, it noted that the art is not required to teach the same reasoning for adding components as Applicant, MPEP 2144 (IV) states "the reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by Applicant. See, e.g., I, 411 F.3d 977, 987, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006)." Applicant further argues that it is only at low levels of paclitaxel that cells exit mitosis, whereas at high levels, cell arrest occurs, and subsequent cell death. Applicant therefore argues that one would not have desired the exit of mitosis but rather cell arrest. Applicant's argument is not found persuasive since paclitaxel is identified in Patel as being "a microtubule-stabilizing agent whose action is concentration dependent" (See Patel, page 4163, first column). Further, Hauf identifies Hesperadin as having a microtubule

stabilizing effect on Taxol treated cells, and Sen teaches that Paclitaxel is useful for the treatment of breast cancer. Therefore, one of ordinary skill in the art would utilize Hesperadin to add to the microtubule stabilizing effect of Taxol in breast cancer patients. Applicant's arguments are not found persuasive since Taxol is identified in Patel as being a microtubule-stabilizing agent, wherein Hesperadin is taught as further stabilizing said microtubules in Taxol treated cells and exiting said cells from mitosis, thereby preventing the cells from proliferating. Applicant further argues that Hauf teaches away from the combination of Taxol and Hesperadin by stating that Hesperadin will override the mitotic arrest induced by Taxol, and therefore act in direct contrast to the intended use of Taxol, which is cell arrest. Applicant's argument is not found persuasive since first, Taxol is identified in Patel as "a microtubule-stabilizing agent", wherein the addition of Hesperadin would increase said effect andcause the cells to exit mitosis, and therefore the breast cancer cells would not continue dividing or growing (see Hauf page 282, 2nd column). While hesperedin overrides Taxol, Hauf does not show that this override causes the cell to proceed through mitosis and continue to grow, rather, Hauf teaches that hesperadin allows the cells to proceed from metaphase to anaphase (e.g., hesperadin overrrides the checkpoint arrest by taxol), however the stabilization of improper microtubule attachments causes these cells to exit mitosis early without cytokinesis resulting in massive polyploidy and, while the cells are able to grow, they do not proliferate (see Hauf page 282, 2nd column). Second it is noted that while a reasonable expectation is required, absolute predictability is not. It is noted that MPEP 2143.02 states "[o]bviousness does not require absolute predictability, however, at least

some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976)". Applicant further argues that Sen only investigates three breast cancer lines, and therefore, one of skill in the art would conclude that *some* breast cancers overexpress Aurora A, not all breast cancers. Applicant's argument is not found persuasive since first, Sen teaches "[o]ur findings suggest that amplification and overexpression of BTAK may be playing a critical role in oncogenic transformation of breast tumor cells" (see Sen, Abstract), second, the high percentage (identified as 18 and 40%) of amplification identified would mean that in at least 18-40% of breast cancers being treated overexpression of aurora A is occurring. Further, the idea or suggestion that the ordinary skilled artisan would not treat those breast cancer cells overexpressing Aurora A (BTAK) makes little sense, given the clear link between Aurora A and oncogenic transformation of breast cancer cells as taught by Sen. Therefore, Applicant's arguments are not found persuasive.

With regard to Applicant's most recent declaration filed 11/11/2010, in assessing the weight to be given expert testimony, the Examiner may properly consider, among other things, the nature of the fact sought to be established, the strength of any opposing evidence, the interest of the expert in the outcome of the case, and the presence or absence of factual support for the expert's opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Development Corp., 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), Paragon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993). In this instant situation, the

nature of the fact sought to be established is whether or not Hesperadin reduces the sensitivity of the cells to Taxol. The significance can be questioned based on the strength of opposing evidence. In the instant case, the data relied upon is a figure in the Hauf reference, and a statement by Hauf that Hesperadin overrides the cell cycle arrest of Taxol treated cells. This argument is based on the assumption that hesperadin will reverse the effects of taxol and presumably the breast cancer cells will proliferate or continue to grow, e.g., proceed through mitosis, however, there is no evidence that this is the case, and to the contrary, Hauf identifies that cells treated with hesperadin do not proliferate. It is noted that Applicant has not provided any evidence, and there is no evidence in Hauf, that hesperadin reverses the effects of taxol and causes cancer cell growth as asserted. In fact, the figures and text of Hauf indicate that hesperadin allows the cells to proceed from metaphase to anaphase (e.g., hesperadin does overrride the checkpoint arrest by taxol), however the stabilization of improper microtubule attachments causes these cells to exit mitosis early without cytokinesis resulting in massive polyploidy and, while the cells are able to grow, they do not proliferate (see Hauf page 282, 2nd column).

However, the teachings of the art that Taxol is a microtubule stabilizing agent (Patel) and Hesperadin further stabilizes Taxol treated cells (Hauf) constitutes strong opposing evidence as to why one would combine the two actives. Finally, it is noted that Ashok Venkitaraman is not only the declarant, but also one of the inventors of the instant Application who has a vested interest in the outcome of the case.

Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Sen et al (1997, Oncogene) as evidenced by Entrez Gene (AURKA Aurora Kinase A) in view of Patel et al (2000, Oncogene) and Hauf et al (2003, Journal of Cell Biology) (IDS reference) as applied to claims 1-5 and 8-9 above, and further in view of Slamon et al (N.E.J.M.).

The teachings of Sen, Patel, and Hauf are set forth above.

Sen fails to directly teach the presence of an antibody which is an aurora A kinase inhibitor.

Slamon teaches that recombinant monoclonal antibody are useful in breast cancer patients to aid in correcting the over expression of HER2 which is over-expressed in 25 to 30% of breast cancers (see Abstract, first eight lines).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize antibodies to mediate the over-expression of aurora A kinase in the breast cancer patients of Sen. One would have been motivated to do so since Slamon teaches the mediation of HER2 over-expression in breast cancer patients by the utilization of antibodies. There would be a reasonable expectation of success in the combination since Applicant identified in the instant specification that there are many well known methods of acquiring antibodies (see instant specification, page 7, lines 1-13). Furthermore, Sen teaches that aurora A kinase is over-expressed in breast cancer patients, and Slamon teaches that antibodies can be used to mediate over-expression of HER2. One would have looked to various options to overcome the aurora A kinase over-expression, such as antibodies. One would have particularly looked to

antibodies since Slamon teaches a method of reducing HER2 gene over-expression by using antibodies (see Slamon (see page 783, last paragraph through 784, first paragraph).

Response to Arguments

Applicant argues in the remarks filed 11/11/2010 that Slamon fails to cure the deficiencies alleged above in Hauf. Applicant's arguments are not found persuasive. See above response to arguments.

Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Sen et al (1997, Oncogene) as evidenced by Entrez Gene (AURKA Aurora Kinase A) in view of Patel et al (2000, Oncogene) and Hauf et al (2003, Journal of Cell Biology) (IDS reference) as applied to claims 1-5 and 8-9 above, and further in view of Obermiller et al (Breast Cancer Res).

The teachings of Sen, Patel, and Hauf are set forth above.

Sen fails to directly teach the presence of a sense or anti-sense nucleic acid which is an aurora A kinase inhibitor.

Obermiller teaches that gene therapy is useful when trying to correct specific molecular defects that contribute to the cause or progression of cancer, specifically, breast cancer (see abstract).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize sense or anti-sense nucleic acids to mediate the over-expression of aurora A kinase in the breast cancer patients of Sen. One would have

been motivated to do so since Obermiller teaches that gene therapy provides the ability to correct specific molecular defects that contribute to the cause or progression of cancer, this would include the over-expression of aurora A kinase in breast cancer patients. There would be a reasonable expectation of success in the combination since Applicant identified in the instant specification that there are many well known methods of down-regulating gene expression. Specifically, the instant specification states "[T]he use of these approaches [sense and anti-sense] to down-regulate gene expression is now well-established in the art (see instant specification, page 8, lines 6-9 and page 10, lines 21-27).

Response to Arguments

Applicant argues in the remarks filed 11/11/2010 that Obermiller and Lange fail to cure the deficiencies alleged above in Hauf. Applicant's arguments are not found persuasive. See above response to arguments.

Conclusion

No claims allowed. All claims rejected. No claims objected.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TREVOR M. LOVE whose telephone number is (571)270-5259. The examiner can normally be reached on Monday-Thursday 7:30-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila Landau can be reached on 571-272-0614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

TL

/David J Blanchard/
Primary Examiner, Art Unit 1643